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The Effects of Tan-Chi-Hsiao-Yao-San on Experimental Hepatotoxicity in Rats

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ABSTRACT

Tan-Chi-Hsiao-Yao-San (丹梔逍遙散, T.S.) is used by Chinese physicians for patients with symptoms similar to those of hepatitis. Clinically, some modern medical studies reported that T.S. was helpful for patients with chronic B hepatitis. The present study was intended to investigate the effects of T.S. on chemical-induced hepatitis in rats. The following results were obtained:

1. **Both alcohol-extracted (T.S. Alc.) and water-extracted (T.S. H_2O) could significantly decrease the serum GOT, GPT, Alkaline phosphatase (AlP), and total bilirubin on acute hepatitis induced by CCl_4.**
2. **Both T.S. Alc. and T.S. H_2O could decrease the serum GOT on subacute hepatitis induced by CCl_4.**
3. **Both T.S. Alc. and T.S. H_2O could significantly decrease the serum GOT, GPT, Alk. phosphatase and total bilirubin induced by D-galactosamine (Gal).**
4. **Both T.S. Alc. and T.S. H_2O could significantly decrease the serum GOT, GPT, Alk. phosphatase, total bilirubin and direct bilirubin induced by α-naphthylisothiocyanate (ANIT).**
5. **Both T.S. Alc. and T.S. H_2O had no apparent effects on praseodymium nitrate [$Pr(NO)_3)_3$]-induced fulminant hepatitis.**
6. **T.S. H_2O has stronger effects than that of T.S. Alc.**
7. **The protective effects of the T.S. preparations were more prominent if given before and after chemical-induced hepatitis.**

INTRODUCTION

Chronic hepatitis and liver cirrhosis is the 6th leading cause of death in Taiwan, R.O.C.[1]. According to the random sampling of blood sample, it was found that in the general population, 90% of people had been infected by hepatitis A virus, 91.3% by hepatitis B virus, and 20% being hepatitis B carrier. The carrier rate of hepatitis B virus is the highest in the world[2]. From the clinicopathological studies, it was shown that in patients with liver cirrhosis and liver cancers, about 3/4 of them were hepatitis B virus carrier[3]. Accompaning the ever-progressing industrialization and econominization, hepatotoxicity due to chemicals, pesticides, heavy-metals, and alcohol had also

become serious problems in Taiwan. Up to now, no definitely proved drugs for both virus and non-virus hepatitis[4]. So looking for effective drugs for hepatitis is a continuing task of pharmacomedical staffs. The ancient Chinese remedy of Tan-Chi-Hsiao-Yao-San is for patients with "liver damage, exhaustion, loss of appetite, and mucocutaneous yellowish discoloration"[5]. All these symptoms are frequently observed in patients with hepatitis.

Up to now, there had been no scientific studies of this remedy on hepatitis. The present study was intended to investigate the effects of this remedy on hepatitis with CCl_4, D-galactosamine, α-naphthylisothiocyanate, and praseodymium nitrate induced hepatitis in rats[6-9].

EXPERIMENTAL

Preparations of Tan-Chi-Hsiao-Yao-San

There are 10 components of this formula: Bupleuri Radix, Angelicae sinensis Radix, Paeoniae Radix, Atractylodis Rhizoma, Hoelen, Glycyrrhizae Radix, Moutan Radicis Cortex, Gardeniae Fructus, Zingiberis Rhizoma, and Menthae Herba. These 10 components were mixed in the ratio of 3:3:4:4:5:2:3:3:1.5:1. Then the mixture was grounded into coarse powder. One kg of the coarse powder was then immersed in 1000 ml 95% alcohol and then evaporated and concentrated in a rotary vacuum evaporator at a temperature around 70°C. The sample was obtained by drying the concentrated at 50°C. The extraction rate was 18%.

In the other preparation (water-extracted), we used water as the solvent. The evaporation and concentration temperature was 90°C and the drying temperature was 60°C. The extraction rate was 30%.

Animals

Male Sprague-Dawley rats, weighing between 190 and 230 g, were used in the following studies. The animals were maintained in groups of 6 per cage at a controlled temperature of 22 ± 1°C and humidity of 55 ± 5% and housed in a metal-wire mesh cage. The solid diet (Fwu Sow solid diet) and tap water were provided ad libitum.

Effects on CCl_4-Induced Acute Hepatitis

CCl_4 was dissolved in olive oil to a 50% solution (v/v) and then given to rats in the dose of 1 ml/kg, i.p. Rats were divided into 10 groups. In the 1st group, only olive oil (1 ml/kg, i.p.) was given. In the 2nd group CCl_4 (1 ml/kg, i.p.) was given. In the 3rd to 6th groups, CCl_4 was given, then T.S. Alc., T.S. H_2O (0.5, 1.0 g/kg) was administered 1 hr and 5 hrs after giving CCl_4. In the 7th to 10th groups, the preparations were administered 1 hr before CCl_4 and then 5 hrs after CCl_4 to see whether the administrations of the T.S. preparations before hand may improve the therapeutic effects. Twenty-four hrs after giving CCl_4, rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) then blood samples for liver function tests were drawn.

Effects on CCl_4-Induced Subacute Hepatitis

CCl_4 was dissolved in olive oil in 50% (v/v), then given to rats in 1 ml/kg, i.p. Rats were divided into 3 groups. In the 1st group, CCl_4 (1 ml/kg, i.p.) was given every 1 week for 8 weeks. In the 2nd;

3rd groups, CCl_4 was given as the same way described for rats in the 1st group, but T.S. Alc., T.S. H_2O (0.5 g/kg, p.o., q.d.) was given from the 3rd to the 8th weeks. Blood samples for liver function tests were drawn every 2 weeks for 8 weeks.

Effects on D-galactosamine-Induced Acute Hepatitis

D-galactosamine (400 mg/kg, dissolved in normal saline, i.p.) was given to rats. Rats were divided into 10 groups. In the 1st group, only normal saline was given. In the 2nd group, D-galactosamine was given. In the 3rd to 6th groups, D-galactosamine was given, then T.S. Alc., T.S. H_2O (0.5, 1.0 g/kg) was administered 1 hr and 5 hrs later. In the 7th to 10th groups, the T.S. preparations were administered 1 hr before D-galactosamine and then 5 hrs after D-galactosamine to see whether the administrations of T.S. preparations before hand may improve the therapeutic effects. Twenty-four hrs after giving D-galactosamine, rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.), then blood samples for liver function tests were drawn.

Effects on α-naphthylisothiocyanate-Induced Cholestatic Hepatitis

α-naphthylisothiocyanate (100 mg/kg, dissolved in 1.5% CMC, p.o.) was given to rats. Rats were divided into 10 groups. In the 1st group, 1.5% CMC solution was given. In the 2nd group α-naphthylisothiocyanate was given. In the 3rd to 6th groups, T.S. Alc., T.S. H_2O (0.5, 1.0 g/kg) was given 5, 13, 21, 29, 37, and then 45 hrs respectively after giving α-naphthylisothiocyanate. In the 7th to 10th groups, T.S. Alc., T.S. H_2O (0.5, 1.0 g/kg) was given 5, 13, 21 hrs before giving α-naphthylisothiocyanate and again 5, 13, 21 hrs after giving α-naphthylisothiocyanate. Forty-eight hrs after giving α-naphthylisothiocyanate, rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.), then blood samples for liver function tests were drawn.

Effects on Praseodymium Nitrate-Induced Fulminant Hepatitis

$Pr(NO_3)_3$ (20 mg/kg, dissolved in normal saline, i.v.) was given to rats. Rats were divided into 3 groups. In the 1st group, $Pr(NO_3)_3$ was given. In the 2nd, 3rd T.S. Alc., T.S. H_2O (1.0 g/kg, p.o.) was administered, 5, 17, 29, 41, 53, 65 hrs, before giving $Pr(NO_3)_3$. Seventy-two hrs after giving $Pr(NO_3)_3$, rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) then blood samples for liver function tests were drawn.

Statistical Analysis

The statistical analysis of the results was performed by means of the Student's *t* test for unpaired data. Results were considered significant if $p < 0.05$.

RESULTS

Erfects on CCl_4-Induced Acute Hepatitis

As shown in Table 1, CCl_4 significantly increased the serum GOT, GPT, Alk. phosphatase, and bilirubin concentrations. T.S. Alc. and T.S. H_2O significantly ameliorated the serum GOT elevations induced by CCl_4. If T.S. preparations were given before and then again after CCl_4, effects on the serum GPT, GOT, Alk. phosphatase, and total biliruin were more prominent. The serum direct

bilirubin levels were not significantly affected by T.S. preparations.

Effects on CCl_4-Induced Subacute Hepatitis

As shown in Table 2, T.S. preparations had protective effect on CCl_4-induced subacute hepatitis.

Effects on D-galactosamine-induced Acute Hepatitis

As shown in Table 3, D-galactosamine significantly increased the serum GOT, GPT, Alk. phosphatase, bilirubin (total and direct) concentrations. T.S. Alc. and T.S. H_2O significantly ameliorated the serum GOT elevations induced by D-galactosamine. If T.S. preparations were given before D-galactosamine and then again after D-galactosamine, effects on the serum GPT, GOT, Alk. phosphatase, and bilirubin prominent.

Effects on α-naphthylisothiocyanate-Induced Cholestatic Hepatitis

As shown in Table 4, all the parameters were increased by α-naphthylisothiocyanate. The T.S. preparations could ameliorate the elevated values. If the preparations given before and then after giving α-naphthylisothiocyanate, they have more significant protective effects.

Effects on Praseodymium Nitrate-Induced Fulminant Hepatitis

As shown in Table 5, the T.S. preparations had no protective effect on $Pr(NO_3)_3$-induced fulminant hepatitis.

DISCUSSIONS

Tan-Chi-Hsiao-Yao-San is used by Chinese physicians for patients with weakness, restlessness, fatigue, anorexia, nausea, vomiting. These symptoms were frequently observed in patients with hepatitis. We investigated the effects of Tan-Chi-Hsiao-Yao-San on experimental hepatitis using various chemicals in rats.

Hepatic injury produced by CCl_4 seems to be mediates by a reactive metabolite – trichloromethyl free radical (CCl_3)-formed by the homolytic cleavage of CCl_4, or by an even more reactive species – trichloro – methylperoxy free radical (Cl_3COO) – formed by the reaction of CCl_3 with O_2. This biotransformation is catalysed by a cytochrome p-450-dependent monooxygenase. The toxicity produced by CCl_4 is thought to be due to the reaction of the free radical with the lipids and proteins. These reactions consequently causes damage to all cellular membranes[10]. We used a single dose to induce acute reversible hepatic damage to simulate an acute hepatitis. Then, multiple doses were used to induce a subacute hepatitis. Both types of hepatitis could be ameliorated by the T.S. preparations and the effects were more prominent if the T.S. preparations were given before and then again after CCl_4. This may imply that the T.S. preparations have protective effects on liver cells.

D-galactosamine was also used to induce acute hepatitis[11]. D-galactosamine may cause hepatic damage by producing galactosamine-l-phosphate and decrease UDP-glucose in liver to decrease glycogen, heteropolysaccharides, and glucuronides productions[12,13] and increase UDP-hexosamine. Because UTP was suddenly difficient, RNA and protein production were decreased[14]. Then, serum

Table 1. Effects of T.S. Extracts on CCl_4-Induced Acute Hepatitis in Rats.

Group	Treatment	Dose (g/kg)	GOT (u/ml)	GPT (u/ml)	AlP (mg/dl)	Bilirubin total (mg/dl)	Bilirubin direct (mg/dl)
1	Olive Oil		137.2±6.0	27.9±1.5	24.3±2.6	0.39±0.02	0.22±0.04
2	CCl_4		976.0±56.5	238.5±29.4	37.2±2.6	1.01±0.06	0.43±0.07
3	CCl_4+T.S.Alc.	0.5	809.5±33.2*	209.0±26.1	36.1±2.5	0.93±0.11	0.42±0.07
4	CCl_4+T.S.Alc.	1.0	630.9±41.6***	188.1±26.7	31.8±2.6	0.96±0.06	0.44±0.06
5	CCl_4+T.S.H_2O	0.5	706.3±39.1***	207.4±21.8	35.4±2.4	1.00±0.05	0.41±0.07
6	CCl_4+T.S.H_2O	1.0	504.5±47.6***	151.4±23.6*	29.3±2.3*	0.91±0.07	0.44±0.07
7	T.S.Alc.+CCl_4+T.S.Alc.	0.5	357.8±35.8***	60.3±5.5***	30.7±2.8	0.86±0.06	0.40±0.06
8	T.S.Alc.+CCl_4+T.S.Alc.	1.0	297.0±35.9***	48.0±4.5***	28.7±2.3*	0.79±0.07*	0.36±0.04
9	T.S.H_2O+CCl_4+T.S.H_2O	0.5	327.3±40.6***	57.0±4.9***	27.4±2.7*	0.82±0.06	0.39±0.08
10	T.S.H_2O+CCl_4+T.S.H_2O	1.0	248.7±47.4***	35.0±3.1***	26.9±2.4**	0.79±0.06*	0.37±0.04

Mean ± S.E. (n = 10)

* : $p < 0.05$, ** : $p < 0.01$, *** : $p < 0.001$ (Compared with CCl_4)

Table 2. Effects of T.S. Extracts on CCl_4-Induced Subacute Hepatitis in Rats.

Group	Treatment	Dose (g/kg)	Weeks	GOT (u/ml)	GPT (μ/ml)	AlP (mg/dl)	Bilirubin total (mg/dl)	Bilirubin direct (mg/dl)
	CCl_4		1	152.0±3.8	29.0±2.2	35.0±4.4	1.35±0.08	0.77±0.09
	CCl_4		2	198.7±9.8	35.5±3.1	46.1±4.9	1.89±0.27	0.40±0.10
1	CCl_4		4	205.7±8.6	39.5±3.1	30.2±4.1	1.84±0.18	0.38±0.05
	CCl_4		6	210.3±3.9	42.0±2.7	49.6±6.8	1.69±0.13	0.35±0.02
	CCl_4		8	201.3±4.7	47.8±1.6	70.4±6.9	1.39±0.01	0.45±0.06
	CCl_4+T.S.Alc.	0.5	4	173.8±7.2*	36.2±2.2	23.2±2.2	1.79±0.27	0.42±0.11
2	CCl_4+T.S.Alc.	0.5	6	170.8±4.4***	40.4±2.7	45.0±4.2	1.69±0.19	0.39±0.22
	CCl_4+T.S.Alc.	0.5	8	196.5±7.0	43.3±1.3	65.2±6.6	1.26±0.04*	0.41±0.08
	CCl_4+T.S.H_2O	0.5	4	171.3±5.5**	31.8±1.9	21.3±4.7	1.64±0.19	0.38±0.08
3	CCl_4+T.S.H_2O	0.5	6	169.8±3.5***	35.8±2.0	26.6±2.9**	1.50±0.07	0.34±0.07
	CCl_4+T.S.H_2O	0.5	8	172.2±5.7**	38.0±1.9**	38.2±8.2**	1.30±0.03*	0.36±0.05

Mean ± S.E. (n = 6)

* : $p < 0.05$, ** : $p < 0.01$, *** : $p < 0.001$ (Compared with CCl_4's, at the 4th, 6th, and 8th week respectively)

Table 3. Effects of T.S. Extracts on D-galactosamine-Induced Acute Hepatitis in Rats.

Group	Treatment	Dose (g/kg)	GOT (u/ml)	GPT (u/ml)	Alp (mg/dl)	Bilirubin total (mg/dl)	Bilirubin direct (mg/dl)
1	Normal Saline		126.5±4.3	24.4±1.0	23.9±2.1	0.39±0.01	0.22±0.04
2	D-galactosamine		894.0±53.1	620.0±63.7	54.0±4.5	1.32±0.05	0.72±0.10
3	Gal+T.S.Alc.	0.5	753.0±41.6	520.1±17.0	51.3±3.5	1.30±0.08	0.52±0.06
4	Gal+T.S.Alc.	1.0	550.0±35.5***	366.4±25.2**	42.5±3.3	1.28±0.07	0.51±0.05
5	Gal+T.S.H_2O	0.5	703.0±30.6**	480.0±20.0	47.2±3.1	1.29±0.09	0.51±0.04
6	Gal+T.S.H_2O	1.0	510.0±37.2***	325.0±25.0***	35.3±4.6**	1.25±0.07	0.50±0.07
7	T.S.Alc.+Gal+T.S.Alc.	0.5	650.0±32.3***	393.0±28.2**	45.2±3.4	1.22±0.08	0.49±0.06
8	T.S.Alc.+Gal+T.S.Alc.	1.0	319.0±33.8***	200.0±26.1	30.0±2.3***	1.00±0.11**	0.45±0.06*
9	T.S.H_2O+Gal+T.S.H_2O	0.5	610.0±34.8***	369.0±26.2**	40.6±4.4*	1.20±0.07	0.48±0.04*
10	T.S.H_2O+Gal+T.S.H_2O	1.0	290.0±37.4***	150.0±23.0***	27.2±2.5***	1.00±0.06**	0.40±0.05*

Mean ± S.E. (n = 10)

* : $p < 0.05$, ** : $p < 0.01$, *** : $p < 0.001$ (compared with D-galactosamine)

Table 4. Effects of T.S. Extracts on α-naphthylisothiocyanate-Induced Hepatitis in Rats.

Group	Treatment	Dose (g/kg)	GOT (u/ml)	GPT (u/ml)	AlP (mg/dl)	Bilirubin total (mg/dl)	Bilirubin direct (mg/dl)
1	1.5% CMC		121.3±6.05	26.4±1.4	23.6±2.0	0.41±0.20	0.25±0.03
2	ANIT		927.0±93.0	715.0±24.2	57.5±3.8	7.01±0.46	6.13±0.48
3	ANIT+T.S.Alc.	0.5	920.0±30.8	652.0±26.2	53.6±4.3	6.79±0.40	5.57±0.45
4	ANIT+T.S.Alc.	1.0	729.0±30.7*	570.0±20.1***	51.9±3.6	6.25±0.41	4.78±0.52
5	ANIT+T.S.H_2O	0.5	830.0±35.1	627.0±26.8*	52.0±3.5	6.40±0.44	4.80±0.58
6	ANIT+T.S.H_2O	1.0	600.0±42.0**	520.0±25.8***	45.5±3.8*	5.97±0.44	4.49±0.44
7	T.S.Alc.+ANIT+T.S.Alc.	0.5	800.0±37.6	530.0±23.9***	48.0±3.0	6.18±0.40	4.89±0.64
8	T.S.Alc.+ANIT+T.S.Alc.	1.0	621.0±45.4**	380.0±23.3***	41.7±4.0**	5.20±0.42*	3.91±0.33**
9	T.S.H_2O+ANIT+T.S.H_2O	0.5	747.9±38.6*	499.0±23.5***	43.2±3.6*	5.59±0.41*	4.17±0.49*
10	T.S.H_2O+ANIT+T.S.H_2O	1.0	504.0±36.0***	350.0±22.5***	39.0±3.5**	4.68±0.39**	3.74±0.36***

Mean ± S.E. (n = 10)
* : $p < 0.05$, ** : $p < 0.01$, *** : $p < 0.001$ (compared with ANIT)

Table 5. Effects of T.S. Extracts on Praseodymium Nitrate-Induced Hepatitis in Rats.

Group	Treatment	Dose (g/kg)	GOT (u/ml)	GPT (u/ml)	AlP (mg/dl)	Bilirubin total (mg/dl)	Bilirubin direct (mg/dl)
1	$Pr(NO_3)_3$		6016.7±404.5	6633.3±562.5	66.2±4.6	6.25±0.56	5.65±0.56
2	T.S.Alc.+$Pr(NO_3)_3$	1.0	6033.3±310.6	5983.3±249.6	54.2±5.1	5.96±0.42	5.17±0.25
3	T.S.H_2O+$Pr(NO_3)_3$	1.0	6000.0±386.4	6266.7±314.8	55.3±3.4	5.98±0.57	5.28±0.46

Mean ± S.E. (n = 6)
Compared with praseodymium nitrate.

COT and GPT concentrations increased. Using this model of hepatic damage, we also found that the T.S. preparations may ameliorate the hepatic damage.

We used α-naphthylisothiocyanate to induce inflammation and proliferation of the biliary tree to simulate the cholestatic hepatitis[15,16]. Then, the T.S. preparations were administered to examine whether these preparations may improve the simulated cholestatic hepatitis and found that the indices of liver function tests were improved by the T.S. preparations.

Praseodymium nitrate hydrate may destroy the hepatic cell reticular endothelium nucleic body, lipid deposition, and loss of biliary tree villus[17]. $Pr(NO_3)_3$ may also interfere the enzyme systems which are associated with Ca^{++}, because praseodymium and Ca^{++} have similar structure and praseodymium has stronger affinity with the enzymes but has no physiological actions of Ca^{++}. We used praseodymium nitrate hydrate to induce a situation similar to fulminant hepatitis. However, we found that the T.S. preparations have no any beneficial effects on fulminant hepatitis.

The T.S. H_2O has more prominent effects than that of T.S. Alc. This may be explained by the fact that saikosaponin, glycyrrhizin, geniposide, glycosides is more dissolved in H_2O.

It has been reported that (1) Bupleuri Radix has anti-inflammatory effect on D-galactosamine induced inflammation[18], (2) the saikosaponin in Bupleuri Radix can decrease the serum GOT, GPT increased by CCl_4[19], (3) glycyrrhizin and glycyrrhetinic in Glycyrrhizae Radix can lower the serum GPT increased by CCl_4 and D-galactosamine[19], (4) glycyrrhizin has antioxidant effect on CCl_4 induced hyperoxidant reactions[19], (5) the geniposide in Gardeniae Fructus can ameliorate the serum GOT, GPT elevations induced by CCl_4, can increase the p-450 activity in hepatacytic microsomes, can activate ATPase, and can enhance Ca^{++} exflux from the intracellular space[20], (6) geniposide may interfere α-naphthylisothiocyanate metabolism to ameliorate the serum GOT, GPT elevations[21] and the crocin, crocetin, genipin, geniposide in Gardeniae Fructus may enhance biliary excretory actions[22-24], (7) Paeoniae Radix, Atractylodis Rhizoma, Glycyrrhizae Radix, Moutan Radicis Cortex, all have antiinflammatory effects[25-27].

From this study, the protective effects of the T.S. preparation on experimental hepatotoxicity may be related to the constituents of each crude herb reported in literatures[18-27].

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中 文 摘 要

丹梔逍遙散對於實驗性肝炎大白鼠之影響

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丹梔逍遙散由柴胡、當歸、白芍藥、白朮、茯苓、甘草、牡丹皮、梔子、薑、薄荷等十味藥材所組成。中醫臨床主治肝鬱火旺而煩熱勞倦、食少嗜臥、肋痛、臍腹脹痛等症，此與肝炎或肝硬化患者之發熱、疲倦、食慾不振、右季肋區痛及腹水等症狀相當。丹梔逍遙散對於肝炎之藥理學研究尚未見報告，故本研究探討其對於肝炎之療效，以對肝臟具有毒性之物質，如四氯化碳、D-galactosamine、α-naphthylisothiocyanate、和硝酸鐠(praseodymium nitrate hydrate)等藥物誘發大白鼠急性、亞急性、膽汁滯留性或猛爆性肝炎，做爲肝炎實驗模式，進行肝功能生化檢驗並探討其效果。由實驗結果顯示，丹梔逍遙散酒精或水抽取物對於四氯化碳引起之急性或亞急性肝炎、D-galactosamine 引起之急性肝炎、α-naphthylisothiocyanate 引起之膽汁滯留性肝炎，均具有改善作用，但對硝酸鐠所引起之猛爆性肝炎無影響。